IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

THERMO FINNIGAN LLC,

Plaintiff and
Counter- Defendant,

v.

APPLERA CORPORATION,

Defendant and
Counter-Plaintiff

Civil Action No. 04-1505-GMS

APPLERA CORPORATION'S OPENING CLAIM CONSTRUCTION BRIEF

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Defendant Applera Corporation ("Applera") submits this opening claim construction brief setting forth its proposed constructions of the disputed terms and phrases of the asserted claims of U.S. Patent No. 5,385,654 ("the '654 patent").

I. NATURE AND STAGE OF PROCEEDING

On December 8, 2004, Thermo Finnigan LLC ("Thermo") brought this action against Applera (assigned Civil Action No. 04-1505-GMS), alleging infringement of the '654 patent.[1] On February 18, 2005, Applera filed its answer and counterclaim seeking, *inter alia*, a declaratory judgment that the '654 patent is invalid, not infringed, and unenforceable for inequitable conduct. By stipulation and order dated January 20, 2006, the Court reset the deadlines for filing opening and answering claim construction briefs. Those briefs are due January 20, 2006 and February 10, 2006, respectively, in accordance with a stipulation submitted by the parties. A claim construction hearing is set for March 16, 2006. Fact discovery is scheduled to close on March 17, 2006. A jury trial is scheduled for March 19, 2007.

II. SUMMARY OF ARGUMENT

Applera's constructions of the claim terms at issue comport with the ordinary meaning that would be ascribed to them by persons of ordinary skill in the art based on

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[1] Thermo filed this suit in response to a suit filed in this Court against Thermo's parent company, Thermo Electron Corp., by Applera and its co-plaintiffs MDS Inc. and Applied Biosystems/MDS Sciex Instruments for infringement of U.S. Patent No. 4,963,736 (assigned Civil Action No. 04-1230). On December 28, 2005, the Court stayed the 04-1230 action along with Thermo's subsequent Civil Action No. 05-110. (D.I. 65 in C.A. No. 05-110). On January 12, 2006, Applera and its co-plaintiffs moved for reargument with respect to the stay of the 04-1230 action (but not the 05-110- action). (D.I. 83 in C.A. No. 04-1230).

their understanding of the invention described in the specification. Thermo's constructions, by contrast, bear no relationship to the actual invention described by the inventors. Thermo proposes broad unsupported meanings of the claim terms in an effort to encompass Applera's DNA Analyzers—devices that made possible the decoding of the human genome, that represent a true scientific leap forward, and that have nothing to do with the invention described in the '654 patent. The Court should reject Thermo's overreaching constructions and construe the disputed terms and phrases in accordance with the '654 patent's description of the invention.

III. STATEMENT OF FACTS

A. The '654 Patent

The '654 patent relates to methods for separating and detecting "anions" in a sample using a chemistry separation technique known as "capillary electrophoresis." The patent purports to address the problem of separating and detecting anions that had been difficult to distinguish using existing methods, and discloses an "improved method" for separating and detecting such anions. The "improved method" involves three techniques, each of which was already known in the art: (1) precise temperature control of the fluid that fills the inside of the capillary, (2) detecting the anions by simultaneously monitoring the sample for absorption of two different wavelengths of light, and (3) the addition of certain "electroosmotic flow modifiers" to control the direction and speed of flow of the fluid in the capillary. (JA 12, 2:22-29, 2:63-68; JA 13, 3:41-46).[2]

[2] "JA __" refers to the Joint Appendix to Claim Construction Brief for U.S. Patent No. 5,385,654.

1. Technological Background: Capillary Electrophoresis

The term "capillary electrophoresis" is defined in prior art U.S. Patent No. 5,066,382 ("the '382 patent"), which the '654 patent incorporates by reference[3] (JA 14, 5:10-14):

> Capillary electrophoresis (CE) is a chemistry separation technique which utilizes the differences in solute electrophoretic velocity to isolate the various components of a sample.

(JA 204, 1:12-15). "Electrophoretic velocity" is velocity of a charged analyte in a buffer solution under the influence of an electric field. (JA 204, 1:42-50). The '654 patent explains that capillary electrophoresis separates components of a sample by "exploiting the different mobilities of sample components in an electric field." (JA 12, 1:18-22).

Figure 1 of the '382 patent (reproduced below) depicts a typical capillary electrophoresis apparatus; (JA 189; JA 204, 2:15-16):

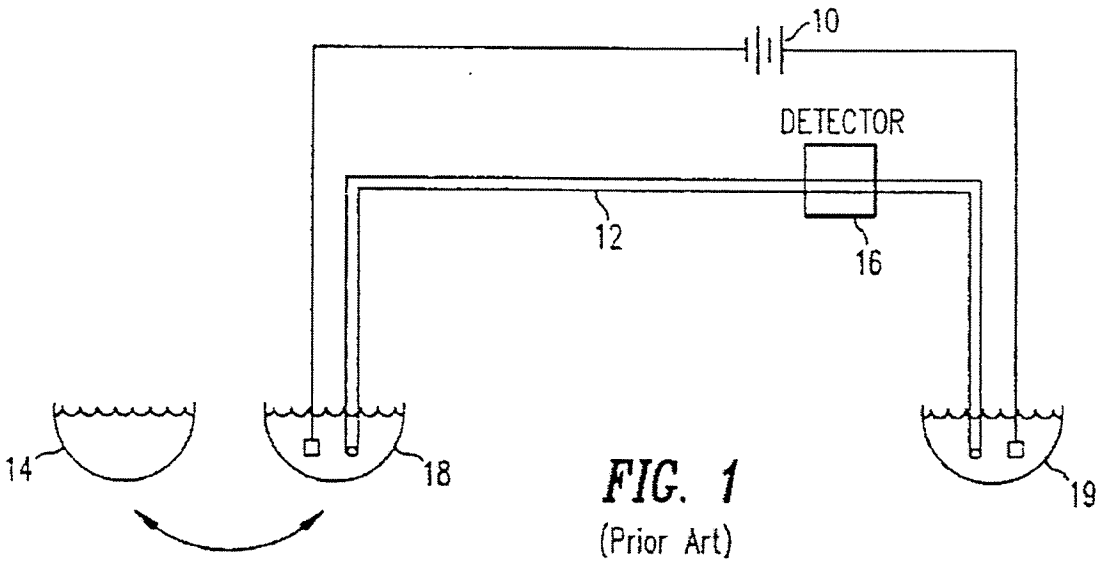

FIG. 1
(Prior Art)

[3] The '382 patent thus forms a part of the specification of the '654 patent. *Advanced Display Systems, Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000); *In re Lund*, 376 F.2d 982, 989 (C.C.P.A. 1967).

Items 18 and 19 represent vials containing a buffer solution. (JA 204, 1:28). The '654 patent refers to the buffer as "carrier electrolyte" and expressly defines "carrier electrolyte" or "buffer" as an "electrically conductive fluid medium." (JA 12, 2:56-57). Vial 14 contains a sample to be analyzed. (JA 204, 1:25).

A capillary tube 12 containing the buffer or carrier electrolyte extends from the first vial 18 (or, alternatively, from the sample vial 14) to the second vial 19. (JA 204, 1:28; *see also,* JA 12, 1:23-25). A high voltage power supply 10 provides an electric field across the buffer-filled capillary, which causes both charged and uncharged particles to move through the capillary. (JA 204, 1:16-24). The capillary electrophoresis system also includes "on-column" detector 16, for "sensing sample zones as they pass the detector." (JA 12, 1:28-30; JA 204, 1:26).

The application of the high voltage electric field across the capillary column causes ions—electrically charged atoms or groups of atoms—to move toward the electrode of opposite charge. (JA 12, 1:30-34). Thus, positively charged ions (cations) migrate toward the negative electrode (the cathode) and negatively charged ions (anions) migrate toward the positive electrode (the anode). (JA 204, 1:44-47). The speed of migration of ions in the sample induced by the application of the electric field depends on "electrical charge, molecular size, mobility of those ions, and/or field strength." (JA 204, 1:33-37; *see also* JA 204, 1:47-50 ("Factors controlling solute electrophoretic velocity are: molecular charge; electrical field strength; viscosity of the migration media; and solute molecular geometric factors.")). Where the different ionic species migrate at different rates, application of the electric field in a system like that disclosed in the '654

patent separates one ionic species from another, facilitating identification of the various ionic species in the sample.

Although neutral molecules are not affected by the electric field *per se*, the application of the electric field causes all of the constituents of the sample to move through the capillary due to a phenomenon referred to as "electroosmotic flow," unless the inside of the capillary is treated or a constituent is added to the carrier electrolyte to eliminate this effect. While the '654 patent does not define electroosmotic flow, the '382 patent, referring to Figure 1 (above), provides a definition:

> Electro-osmotic flow is the bulk flow of buffer from a first buffer vial 18 to a second buffer vial 19 through capillary 12 due to the shearing movement of a diffuse layer of cations past a more firmly held, dense layer, interacting with integral, anionic groups of the capillary wall.

(JA 204, 1:27-32). Thus, at the time the '654 patent application was filed, electroosmotic flow was understood to mean the flow of the buffer caused by the migration of positive ions (cations) toward the cathode over another layer of cations bound to negatively charged groups (anions) on the capillary wall. The '654 patent discloses the use of small cationic molecules that bind to and neutralize the negative charge on the capillary wall thereby eliminating, diminishing, or potentially reversing electroosmotic flow. (JA 12, 2:63-3:4). The speed at which a particular substituent migrates through the capillary is determined by adding its electrophoretic velocity, *i.e.*, the speed induced by the electric field, to the velocity imparted by electroosmotic flow.[4] (JA 204, 1:51-53).

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[4] The electroosmotic flow may be in the same or opposite direction of the electrophoretic velocity, and the sum is therefore a directional sum of both.

2. The Asserted Claims

Thermo asserts claims 11 and 15 of the '654 patent against Applera's family of DNA analyzers. (Plaintiff's Response to Interrogatory No. 2, A 2 – A 3).[5] With the disputed terms addressed by the parties underlined for emphasis, those claims read as follows:

> 11. A method for detecting and separating anions in a sample using capillary electrophoresis comprising the steps of, providing a capillary filled with a carrier electrolyte, heating or cooling said capillary to a target temperature in the range of from 20° to 60° C., introducing a sample containing one or more anions into said capillary, applying an electrical current to said capillary under conditions causing anions in said sample to migrate and separate, and detecting said anions by simultaneously monitoring said sample at two different wavelengths while maintaining the temperature in said capillary to within ±0.5° C. of said target temperature.
>
> 15. The method of claim 11 including the step of including an electroosmotic flow modifier in said carrier electrolyte.

(JA16, 9:35-10:2, 10:12-14) (emphasis added).

3. The '654 Patent's Description of the Invention

a. The Problem Addressed: Some "Small Analytes" are Difficult to Distinguish Because They Do Not Absorb UV or Visible Light and They Migrate at Similar Rates

The '654 patent frames the problem that the invention addresses by first explaining that capillary electrophoresis "is a powerful and efficient method to separate small analytes[6] at very low concentrations by exploiting the different mobilities of sample

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[5] "A __" refers to the Appendix to Applera's Opening Claim Construction Brief, which accompanies this brief.

[6] An "analyte" is "the substance being identified and measured in an analysis." Academic Press, Dictionary of Science and Technology (Morris, ed., 1992) at 105 ("Dictionary of Science and Technology") (A 10). The analytes measured in the '654 patent are anions.

components in an electric field." (JA 12, 1:18-22). The problem, according to the patent, is that some analytes are difficult to distinguish for two principal reasons. First, "many analytes, including most inorganic ions, do not absorb ultraviolet or visible light," and will therefore pass by a detector that measures the absorption of ultraviolet/visible light "without being observed." (JA 12, 2:38-43). The specification explains that such non-absorbing ions could be detected using the known technique of "indirect photometric detection," which utilizes the presence of a light-absorbing electrolyte or co-anion in the sample. (JA 12, 1:66-2:6). Indirect photometric detection involves measurement of the absorption of light by the light-absorbing electrolyte in the carrier electrolyte, not absorption by the ion of interest. (JA 12, 1:43-49). Using this technique, the presence of an ion of interest is demonstrated by a decrease in absorbance of light by the carrier electrolyte as the anion passes the detector. (JA 12, 1:50-65).

According to the patent, although indirect photometric detection permits detection of non-absorbing ions, a second issue persists—that certain ions are difficult to separate from others because they have similar migration rates through the capillary and similar transparency to or absorbance of ultraviolet light. (JA 12, 2:6-10).

Thus, the patent states that a need exists to improve separation and detection of small concentrations of ion species, "especially those which are nonabsorbers of light." (JA 12, 2:15-19). "The present invention meets those needs by providing an improved method for the separation of *anions* using capillary electrophoresis techniques. Both organic and inorganic anions may be separated." (JA 12, 2:22-25) (emphasis added). The patent specifically identifies "low molecular weight anions" as the anions at issue:

> The present invention is particularly suited to detect such common *low molecular weight inorganic and organic anions* such as chloride, nitrate,

> nitrite, sulfate, and oxalate. Many of these anions have been difficult to detect using conventional CZE techniques in the past because they do not absorb significant amounts of light at many wavelengths in the ultraviolet range. The present invention also provides for the detection of such other common organic anionic species as tartrate, malate, succinate, lactate, acetate, propionate, butyrate, citrate, and caprylate. The use of light-absorbing co-anions in a preferred embodiment which are displaced as the other anions in the sample migrate, permits their presence to be detected as an absence of UV light absorption or a negative peak monitored on the photodetector.

(JA 13, 3:5-20) (emphasis added).

b. The Patent Discloses Precise Control of the Temperature of the Fluid Inside the Capillary Column to Improve the Ability to Distinguish Anions in a Sample

As one aspect of the "improved method" of separating and detecting "low molecular weight inorganic and organic anions," the patent discloses "[u]sing precise control of the temperature of the fluid in the capillary column, [such that] the migration speed and order of migration of the anions may be controlled to improve the selectivity of the process." (JA 1, Abstract). The patent explains that the viscosity of the electrolyte solution is influenced by temperature, and that close temperature control prevents changes in viscosity and thus allows a high degree of reproducibility.[7] (JA 12, 2:30-35; JA 13, 3:21-28; JA 14, 6:3-6, 6:17-19; JA 15, 7:27-29, 7:64-65).

To achieve this end, the patent discloses heating or cooling the fluid that fills the capillary to a "target temperature," introducing a sample into the capillary, applying an electric field to the capillary, and detecting the anions, "while maintaining the

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[7] The influence of temperature and heating in the capillary tube due to the application of the electric field during electrophoresis was well understood at the time the '654 patent application was filed. *See e.g.,* Gobie and Ivory, "Thermal Model of Capillary Electrophoresis and a Method of Counteracting Thermal Band Broadening," 516 Journal of Chromatography 191 (1990) at 191-193 (A 14 – A 33); Jones and Grushka, "Nature of Temperature Gradients in Capillary Zone Electrophoresis," 466 Journal of Chromatography 219 (1989) (A 34 – A 40).

temperature in the capillary to within ±0.5° C. of the target temperature." (JA 204, 2:36-47). According to the patent, proper selection of a target temperature and precise control of the temperature of the fluid in the capillary column to within ±0.5° C of the target temperature allows the speed and order of migration and selectivity of the anions' separation to be precisely controlled and ensures a high degree of reproducibility:

> By proper selection of a target temperature which is different from ambient temperature and which may be higher or lower than ambient, and closely controlling the temperature of the fluid in the capillary column to within ±0.5° C., and most preferably to within ±0.1° C., these anionic species may be separated and detected at very low concentrations of less than 1 ppm, and preferably less than 100 ppb. A preferred target temperature is in the range of from about 25° to 60° C. At a selected temperature within that range, the speed and order of migration, and thus the selectivity of the separation of the anions may be precisely controlled.
>
> * * *
>
> Additionally, precise temperature control provides a high degree of reproducibility for the process.

(JA 13, 3:21-40). The '654 patent makes clear that the temperature of the fluid throughout the capillary must be maintained to avoid the heating effects on the viscosity of the electrolyte in order to achieve a high degree of reproducibility. (*See e.g.*, JA 14, 6:17-19).

The patent describes controlling the temperature in the capillary "to within ±0.5° C., and preferably to within ±0.1° C" using "an automated capillary electrophoresis instrument such as a SpectraPHORESIS® 1000 commercially available from Spectra-Physics Analytical, Inc.," the predecessor of the assignee named on the face of the '654 patent. (JA 14, 5:3-10). The '654 patent states that the operation of the thermal control for the SpectraPHORESIS 1000 is described by the '382 patent and it incorporates that patent by reference:

> Operation of the thermal control for such a capillary electrophoresis instrument is described by Weinberger et al. in U.S. Pat. No. 5,066,382, the disclosure of which is hereby incorporated by reference.

(JA 14, 5:10-14).

The '382 patent discloses a method for operating a capillary electrophoresis device at a stable predetermined temperature (JA 204, 1:58-2:3; 2:23-46), and, in particular, addresses the difference between the temperature of the medium (*e.g.*, air) surrounding the capillary tube and the temperature of the sample inside the capillary. (JA 205, 3:33-49). The temperature in the capillary during electrophoresis is controlled by monitoring the electrical resistance across the capillary and maintaining it at a constant level by adding or removing heat from the medium surrounding the capillary (*e.g.*, by flowing cool air across the capillary). (JA 206, 5:8-18). A set temperature ("target temperature") is selected and the capillary tube is allowed to equilibrate until the temperature of the capillary approaches (*i.e.*, becomes "very close" to) the temperature of surrounding air. (JA 209, 11:65-12:5). A sample is introduced into the capillary. An electric field is then applied that does not produce significant heating, but allows calculation of an average electrical resistance (of the fluid in the capillary) at the set temperature. (JA 209, 12:6-20). The electric field is then increased to begin electrophoresis. The resistance across the capillary is monitored and heat is either pumped into or out of the chamber surrounding the capillary as necessary in response to changes in the resistance. "*Thus the electrical resistance of the capillary is maintained at a constant level, providing a constant temperature.*" (JA 209, 12:25-34) (emphasis added); (*see also* JA 207, 7:63-8:9). The '654 patent discloses no other means of maintaining the temperature in the capillary to within ±0.5° C of the target temperature.

c. The Patent Discloses Simultaneous Monitoring of a Sample for Absorption at Two Wavelengths

The patent describes another aspect of the "improved method" for separating and detecting anions: "In another embodiment, anions in a sample may be detected by simultaneously monitoring the sample at two different wavelengths with the photodetector." (JA 13, 3:41-44). The patent explains that "[t]his method takes advantage of the behavior of nitrogen-containing anions such as nitrates, nitrites and thiocyanates." These anions strongly absorb ultraviolet light at one wavelength, but not at another. Thus, if absorption at two wavelengths is monitored simultaneously as these anions pass by, the detector will detect these anions by a positive absorption peak at one wavelength (the absorbed wavelength) and a negative peak at the other wavelength (the unabsorbed wavelength). In this way, a "unique signature" for nitrogen-containing anions is provided:

> In another embodiment of the invention, anions in a sample may be detected by simultaneously monitoring the sample at two different wavelengths with the photodetector. This method takes advantage of the behavior of nitrogen-containing anions such as nitrates, nitrites, and thiocyanates. In this embodiment, the sample is monitored at wavelengths of 210 and 254 nm simultaneously. Nitrate and nitrite strongly absorb at 210 nm, but not at 254 nm. Thus, a strong positive peak occurs at the lower wavelength, while a negative peak is simultaneously observed at the higher wavelength. These unique signatures permit ready identification of nitrogen-containing anions.

(JA 13, 3:41-53; *see also* JA 14, 6:26-42).

Example 1 of the patent employs the prior-art commercially available SpectraPHORESIS 1000 to carry out a method falling within the scope of claims 11 and 15. The SpectraPHORESIS 1000 included a multiple wavelength analysis mode that enabled monitoring a sample for absorption of two wavelengths simultaneously. Example 1 discloses the use of the SpectraPHORESIS 1000's UV/visible light detector to

monitor absorption at 210 nm and 254 nm simultaneously. (JA 15, 7:24-26). Figures 1A-E of the '654 patent demonstrate the resulting spectra of simultaneous positive and negative absorption deflections for the nitrate and nitrite ions and the negative deflections for the remaining anions that were tested in Example 1. (JA 2 – JA 6; JA 15, 7:27-40).

The '654 patent makes clear that the reference in claims 11 and 15 to "monitoring two wavelengths simultaneously" refers to monitoring *absorption* at two wavelengths simultaneously. No other means of monitoring "wavelengths" is described, enabled, or even mentioned in the patent. As discussed below, this point was emphasized by the inventors during the prosecution of the patent.

d. The Patent Discloses the Use of Small Cationic Molecules to Control Electroosmotic Flow

Another aspect of separating the anions addressed in the '654 patent is the addition of certain known electroosmotic flow modifiers to control the direction and speed of flow of the fluid in the capillary. The '654 patent acknowledges that "there are many known electroosmotic flow modifiers in the art," and from those "many," the '654 patent discloses the use of a subset, which it characterizes as "preferred":

> While there are many known electroosmotic flow modifiers in the art, preferred electroosmotic flow modifiers for use in this invention include diethylenetriamine (DETA) and aliphatic trimethyl ammonium halides or hydroxides such as tetradecyltrimethylammonium bromide (TTAB).

(JA 14, 5:37-42; *see also* JA 12, 2:67-3:4). Each of the examples in the '654 patent includes the use of DETA or TTAB.

B. The Prosecution History of the '654 Patent

During prosecution, the examiner rejected the claims at issue under 35 U.S.C. § 102 as anticipated by U. S. Patent No. 5,104,506 to Jones *et al.* ("Jones") (JA 212 – JA

218), or, alternatively, under 35 U.S.C. § 103 as obvious over Jones in view of a publication by Morin *et al.*, "Separation of Arsenic Anions by Capillary Zone Electrophoresis with UV Detection," 342 Fresenius Journal of Chemistry 357 (1992) ("Morin") (JA 65 – JA 70). The examiner found that Jones discloses the use of capillary electrophoresis to separate and detect anions using indirect photometric detection of ions, and disclosed the use of the same electroosmotic flow modifier identified for use in the '654 patent. The examiner acknowledged that Jones is silent regarding the temperature of the analysis, but presumed that it was conducted at ambient temperature, which the examiner found inherently falls within the claimed temperature range. (JA 59).

With regard to obviousness, the examiner stated that Morin "teaches that the temperature can effect [sic] the quality of the separation of anions using capillary zone electrophoresis and how to maintain the capillary at a specific temperature is known in the art." (JA 61). The examiner concluded that it would have been obvious to optimize the temperature when performing the method disclosed by Jones because "the criticality" of temperature was known. (JA 61).

In response, the inventors argued that Jones does not teach "heating or cooling of a capillary" to the recited range of temperatures, or "simultaneous monitoring at two different wavelengths." (JA 122 – JA 123) (emphasis in original). The inventors asserted that claim 14 (now claim 11 of the '654 patent) was not anticipated for that reason. (JA 123). With regard to obviousness, the inventors distinguished the claims at issue from Morin because Morin "*does not relate to an indirect absorbance detection system.*" (JA 122) (emphasis added). In addition, the inventors argued that a person of skill in the art would not conclude from Morin that temperature was a "critical parameter" as suggested

by the examiner. (*Id.*). The examiner therefore allowed claims 11 and 15 without further substantive argument by the applicants.

The '654 patent issued January 31, 1995, however, Thermo allowed the '654 patent to expire by failing to pay the maintenance fee due on January 31, 2003. According to Thermo, it allowed the patent to expire because Thermo was no longer in the capillary electrophoresis business and it was unaware of Applera's alleged infringement. (Plaintiff's Response to Interrogatory Nos. 5 and 16, A 4 – A 7). Nevertheless, the decision to drop the patent rather than to pay the modest fee required to maintain it speaks volumes about the worth and importance of the invention.

C. The Accused Devices: Applera's DNA Analyzers

Thermo alleges that Applera's family of DNA analyzers infringes claims 11 and 15 of the '654 patent. Applera's DNA analyzers, in particular the Prism 3700 DNA Analyzer named in Thermo's complaint, revolutionized the field of genome mapping. It was the primary tool used to decode the human genome.[8] The Prism 3700, which was released in 1998, provided 96 capillaries and a flowable polymer network that allowed separation of DNA strands. The Prism 3700 detected individual DNA and allowed sequencing of DNA strands by using a unique set of four fluorescent tags applied to the nucleotides that make up a strand of DNA. Each of these tags emits a different color of fluorescent light upon exposure to a laser, thereby permitting decoding of the nucleotide sequence. The accused devices changed an entire field of science; in contrast, the '654

[8] *See e.g.*, Pennisi, "The Human Genome," Science, Feb. 16, 2001, at 1179 (*see* sidebar, "Unsung Hero: Mike Hunkapillar") (A 41).

patent was so inconsequential that Thermo let it lapse rather than part with the nominal maintenance fee required to keep it in force.

IV. ARGUMENT

A. "Anions"

Claim Term	Applera Construction	Thermo Construction
anions	Low molecular weight monomeric negatively charged ions.	Negatively charged ions.

"Anions" is a technical term. In its broadest usage, an "anion" is a "negatively charged ion, which is attracted to an anode."[9] However, as used in the '654 patent, the term "anion" has a special and more narrow meaning. The '654 patent does not describe the separation and detection of all anions in the broadest sense of the term. Instead, the specification describes separation and detection of only low molecular weight monomeric negatively charged ions.

"[T]he best source for understanding a technical term is the specification from which it arose, informed, as needed, by the prosecution history." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (citations omitted). "Ultimately the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." *Id.* at 1316 (quoting *Renishaw PLC v. Marposs Societa' per Anzioni* 158 F.3d 1243, 1250 (Fed. Cir. 1998)). In *Phillips*, the Federal Circuit reiterated the often-followed principle, which applies here, that "the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess." *Id.* The

[9] Dictionary of Science and Technology at 118 (A 11).

special meaning does not need to be explicitly stated. *Astrazeneca AB v. Mutual Pharmaceutical Co., Inc.*, 384 F.3d 1333, 1339-1340 (Fed. Cir. 2004) (citing *Bell Atlantic Network Services, Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) (claim terms may be defined without an explicit statement of redefinition)).

The very first sentence of the specification states: "The present invention relates to the separation and detection of *common anionic species* using capillary electrophoresis." (JA 12, 1:6-8) (emphasis added). In the next paragraph, the specification states that "[c]apillary zone electrophoresis is a powerful and efficient method to separate *small* analytes at very low concentration levels." (JA 12, 1:18-20) (emphasis added). The first sentence in the "Detailed Description of Preferred Embodiments" again identifies the anions to which the method of the invention is directed are "common inorganic and organic anionic species":

> The present invention utilizes capillary electrophoresis in conjunction with precise temperature control to achieve improved separation and detection of *common inorganic and organic anionic species*. The preferred method of detecting *such anions* . . . .

(JA 13, 4:31-34) (emphasis added).

In the "Summary of the Invention," the specification identifies the kind of analyte that is "small" and constitutes a "common" anionic species, stating that "[t]he present invention is particularly suited to detect such common *low molecular weight* inorganic and organic anions such as chloride, nitrate, nitrite, sulfate, and oxalate." (JA 13, 3:5-7). This description is reiterated in the "Detailed Description of Preferred Embodiments." (JA 14, 5:44-48). Every anion listed or exemplified in the '654 specification is a low molecular weight ion. (JA 12, 2:60-63; JA 13, 3:7-8, 3:13-15; JA 14, 5:20-31, 5:46-47,

6:8-10, 6:47, 6:52-54; JA 15, 7:11-12, 7:48; 8:30-32). The specification consistently illustrates "anion" only with respect to low molecular weight anions.

The specification and the prosecution history also consistently use the term "anion" to refer to "monomeric" (or "monomer-like") anions, *i.e.*, anions similar to or resembling a "monomer."[10] The '654 patent neither discloses nor alludes to separation and detection of polymeric anions, oligomeric anions, DNA, RNA, or anything of the like. The patent describes only monomer-like anions: simple, non-polymeric anions. The inventors describe the invention as relating to separation and detection of lists of inorganic and organic anions (*see e.g.,* JA 12, 2:60-63), all of which are monomeric, *i.e.*, monomer-like, not polymeric.

During prosecution, the inventors emphasized that their invention relates to separation and detection of small monomeric anions. The inventors submitted three references to the Patent Office that they claimed to constitute "joint work" on the invention "described and claimed" in the patent application. Each of the references describes separation and detection of small monomeric analytes.

An August 1992 research disclosure describes the separation of "small anions" using indirect photometric detection to monitor simultaneously "absorption" of UV light at two wavelengths. It discloses the separation and detection of chloride, sulfate, oxalate, nitrate and nitrite—all of which are small, "monomeric" anions. (JA 98). A second research disclosure dated August 1992 describes capillary zone electrophoresis as a powerful tool for separating "small analytes," and demonstrates the use of the technique to separate the anions oxalate, tartrate, malate, succinate, lactate, acetate, propionate,

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[10] "Monomeric" means "relating to, characteristic of, or resembling a monomer." *See e.g.,* Dictionary of Science and Technology at 1409 (A 13).

butyrate and caprylate, all of which are monomeric. (JA 99-100). In a 1993 paper, two of the inventors describe the use of capillary electrophoresis and indirect photometric detection to detect organic acids and inorganic anions. (JA 102-103). The paper states that separation of "low molecular weight anions" had been addressed in the prior art, but that the work described in the paper provided data on the influence of temperature on such separations. (JA 104). The 1993 paper discloses detection of oxalate, tartarate, malate, succinate, lactate, propionate, caprylate, chloride, sulfate, nitrite, oxalate, nitrate, chlorate, and bromate, all of which are small and monomer-like.

To overcome these references, the inventors submitted a joint declaration asserting that each of the publications describes joint work on "the invention described and claimed in our '439 patent application":

> While we did not jointly coauthor each of the publications listed above, those articles describe our joint work on *the invention described and claimed* in our '439 patent application. Thus, all of the authors listed contributed to *the subject matter which we jointly disclose and claim in our '439 patent application*.

(JA 124-125) (emphasis added). Thus, the inventors unequivocally averred during prosecution that the "invention" claimed in the '654 patent is the separation and detection of low molecular weight monomeric anions. Such a clear and unmistakable statement regarding the claimed invention limits the construction of the claims. *See e.g., Wang Laboratories, Inc. v. America Online, Inc.*, 197 F.3d 1377, 1384 (Fed. Cir. 1999); *see also, Phillips*, 415 F.3d at 1316.

A person skilled in the art would understand that the disclosed invention is limited to separation and detection of low molecular weight monomeric anions. Therefore, although the term "anion" generally has a broad meaning, the inventors used the term more narrowly in the context of the '654 patent.